Remarks/Arguments

The foregoing amendments include the replacement of the title with a more specific title, and the amendment of claims 1, 5, and 23. The amendments in claims 5 and 23 are of formal, grammatical nature. Support for the amendment of claim 1 is at least at page 10, lines 13-17 of the specification. The amendments do not add new matter.

Rejections Maintained

In the final Office Action mailed on December 3, 2002, the Examiner maintained the rejection of claims 1-2, 4-6, and 23 under 35 U.S.C. 103(a) as allegedly unpatentable over Caras (WO 96/13518, May 1996) in view of Wang et al. (Cell, Vol. 93, pages 741-753, May 29, 1998, IDS) "for the reasons of record (see Paper Nos: 12 and 8)."

The rejection, again, is respectfully traversed. In order to avoid unnecessary repetitions, Applicant's prior arguments are hereby expressly incorporated by reference, while the Examiner's new assertions are addressed below.

Applicant has earlier submitted that the combination of Caras and Wang et al. was legally improper for lack of motivation, in view of the differences between the EphA receptors and their ligands (which are the focus of the Caras publication) and the EphB receptors and their ligands (which are the focus of the Wang et al. paper). In attempting to rebut this argument, the Examiner notes that "despite the fact that these molecules are considered fundamentally different, they both elicit effects on angiogenesis." The Examiner refers to a statement from Wang et al. that Eph-A-class receptors and their ligands have "also been implicated in angiogenesis," and that "ephrin-A1 has been shown to promote angiogenesis in vivo as well as endothelial chemotaxis," to provide motivation to combine the two references.

Applicant submits that the Examiner's current argument lacks solid legal or scientific foundation, since it is based on an out of context citation from Wang et al. At page 749, first column, Wang et al. indeed state that "Eph-A-class receptors and their ligands have also been implicated in angiogenesis." However, this sentence is followed by the following explanation:

> Human umbilical vein endothelial cells (HUVECs) express Eph-A2, and TNF-α-induced angiogenesis is mediated by ephrin-A1 in vivo (Panday

> et al., 1995). *Eph-A2* mutants, however, do not exhibit any detectable phenotype (Chen et al., 1996). We have not yet explored the expression of Eph-A-class receptors and their ephrin-A-class ligands on embryonic arteries and veins in vivo. However, the phenotype of the *ephrin-B2* mutant in the yolk sac, head, and heart suggests that there is not [sic] substantial functional redundancy of ephrin ligands in these regions of the embryonic stages we have examined. Nevertheless, other ephrins and their receptors could be expressed in different vessels or vascular beds at different stages of development or in the adult (Stein et al., 1998).
> (Page 749, passage bridging columns 1 and 2.)

The entire paragraph clearly shows that from the prior observation that EphA receptors have also been implicated in angiogenesis, the authors do not conclude that EphA and EphB class receptors would be functionally equivalent or play analogous roles in angiogenesis. On the contrary, the passage, when cited in whole, teaches that the EphA and EphB receptors are likely to play significantly different roles in angiogenesis ("there is [no] significant functional redundancy of ephrin ligands," and "ephrins and their receptors can be expressed in different vessels or vascular beds at different stages of developments or in the adult"). In addition to the fact that the EphA and EphB receptors "are considered fundamentally different," which the Examiner has admitted, they are also expected to elicit fundamentally different effects on angiogenesis, which were yet to be discovered at the time the cited references were published. Accordingly, the combination of Caras and Wang et al. is just as inappropriate as would be the combination of a reference describing another structurally and functionally distinct angiogenic factor, such as VEGF, with either Caras or Wang et al. The statement that "ephrin-A1 has been shown to promote angiogenesis in vivo as well as endothelial chemotaxis" (page 750, 2nd column, 2nd paragraph), which is also cited in the Office Action, does not make the purported combination of references any more appropriate. Again, from the existence of another, structurally and functionally distinct, molecule (ephrin-A1) which was described to be involved in angiogenesis at the time the present invention was made, a person skilled in the art could not draw any conclusion about the function of EphB receptors and ephrin B ligands involved in the present invention. Accordingly, Applicant maintains that the combination of Caras and Wang et al. is legally improper.

Applicant also maintains that the references, even if they could be properly combined, do

not make obvious the present invention. An expert Declaration in support of this argument is in preparation and will be submitted shortly.

It is believed that in view of the foregoing arguments, and the Declaration to be submitted, the Examiner should find all claims allowable. Therefore, the issuance of a Notice of Allowance is respectfully solicited.

Should the Examiner find that there are any further issues outstanding, Applicants hereby request a personal interview. The Examiner is respectfully requested to contact the undersigned attorney to arrange the time for the interview.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39766-0104A). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 2, 2003

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